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Unravelling the controversies surrounding host immune response to helminth and malaria parasites

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Introduction

Humans are hosts to nearly 300 species of parasitic worms; which have co-evolved over hundred million years, with over 70 species of protozoa including malaria parasites [1,2]. Commonly, helminth and malaria cause great impact in terms of mortality, morbidity and contributions to the Quality/Disability Adjusted Life Years (QALYs/DALYs) [3] of their hosts. Since communication in the immunological labyrinth involves cells, cytokines and antibodies together with host natural defense mechanisms, it is important to understand the mechanisms that might be involved in hosts response to helminths and malaria coinfections [4], a knowledge paramount in the control of these infections. How much of influence does the environment have on the level of immune response to an infection needs to be unraveled? Why do I say this?

Humoral and Cell mediated Immunity in Infection

Apart from the innate immune response involved in fighting against all infections, the adaptive immune response which comprises antibodies (humoral) and cell mediation (T cells) is vital to successfully stop infection from being established [5]. When T-cell Receptors complexes with MHC I or II with peptide of processed antigens on an Antigen Presenting Cell (APC), coupled with CD3 activation, the cells proliferate and differentiate targeting the antigen [1,5-8] for a successful clearance. The outcome of the effector cells produced from such activations are dependent on the cytokine *milieu* of the host, and this environment is largely influenced by the phenotypes of the genes of the T-cell regulatory factors. The complex life cycles of helminth and malaria parasites in their hosts obviously affect the T-cell proliferation and differentiation pathway. One important question that remains unanswered is whether one can just categorize the two infections into the Th1 and Th2 arms as have been tried previously?

Helminth immunology

Hookworms survive relatively well in an immunologically hostile environment, although the Th2 phenotype is associated with partial protection. The parasite may promote its survival by secreting a molecular screen of immune- suppressive agents and, possibly, by stimulating the appearance of regulatory T-cell populations [9,10]. Hookworm has the capacity to downregulate the FcεR1 on basophils and mast cells which in turn explains the protective effect in hookworm infection against environmental allergens and responses that lessens the detrimental effects in autoimmunity [9,11,12]. Fortunately, Pritchard et al, 2007 showed that from a parasitological standpoint, potentially protective FcεRI-dependent immune responses are not blocked in hookworm infection but rather mediated by secreted parasite immune suppressants and the induction of regulatory leukocyte populations [13].

In a Schistosome-endemic area, egg-positive people had significantly higher levels of specific antibodies and IFN-γ in contrast to egg negative individuals that had significantly higher circulating IL-4, IL-13 and IL-21 [14]. Previous studies suggesting that anti-helminth immune responses fall into a Th1 (pro-inflammatory) and Th2 (anti-inflammatory) dichotomy with resistance to infection being associated with Th2 responses failed to fully explain resistance, susceptibility to infection and re-infection in people resident in helminth endemic areas. For example, both Th1 and Th2 responsiveness appear compromised in schistosomiasis patients, and within the Th2 compartment, IL-5 responses were suppressed while IL-4 production was relatively intact [15]. There is no clear pattern between Th1 or Th2 cytokine responses and infection intensity. The existence of a regulatory subset of T-cells (Treg), which modulate the effects of Th1 and Th2 responses through the immunosuppressive cytokines interleukin-10 (IL-10) and transforming growth factor beta (TGFβ) have been characterized [16-18]. The balance between Th1, Th2 and Treg responses determine the outcome of helminth infections [14,16-18] a process largely attributed to the plastic nature of T-cells.

Plasmodium species immunology

Malaria pathogenesis is complex and this mostly involves immunologic and non-immunologic mechanisms. In malaria parasite immunology, humoral immune response is elicited to the extracellular stage and cell mediated immune (CMI) response; involving largely T-cells, to the intracellular phase of the parasites' development [5] with the involvement of some peripheral blood cells and lymphocyte subsets [8]. It has been alluded that CD4+ T-cell responses are associated with controlling the intracellular phase of malaria parasites' infection [5]. But since the parasite biology and kinetics at the various stages of the life cycle differ significantly, one would expect the immune response elicited to the parasite stages to be dissimilar and even if CD4+ plays a

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significantly role, it might be in a different subset bearing in mind the concept of CD4+ T-cell plasticity [5,16,18]. Little has been documented of the very role CD4+ T-cells play in the immune response to the pre-erythrocytic stage of malaria parasite infection. But because of records of antibodies in vaccination [6,19], which indicate response to antigens of the extracellular stage, such as circumsporozoite protein (CSP) used for RTS,S malaria vaccine and liver-stage antigen 1 (LSA1), the involvement of CD4+ cells in receiving antigens from APCs and activating B-cells cannot be discounted [6,20]. Another form of T-cells, *TCR-γδ* cells which make up 1%-10% of circulating lymphocytes in human exhibit marked increase in human *Plasmodium spp* parasite infections, which could remain elevated for more than a month even after treatment [8,20]. *TCR-γδ* play important cytotoxic role in malaria parasite infection [20], operate through cytolytic and proinflammatory molecules, their increase correspond to an increase in IFN-γ produced by T-bet+ Th1 cells, Natural Killer (NK) cells, natural regulatory cells (Tregs; to suppress immune reaction), natural killer T (NKT) cells and CD8+ T-cells [6,20].

Basically, Th1/Th2 paradigm has been proposed to fight against malaria infection in human and this has not been enough to explain the immune response put forward in infected people. Follicular CD4+ T (Tfh) cells producing IL-21 cytokines have been reported in immune adults living in endemic areas of *Pf*. Though activation of Th17 subset of CD4+ cells producing IL-17A cytokine occurs, there have not been any identified and defined role during *Plasmodium* infections [5,16,18]. The regulatory T-cells are extremely important to control the inflammatory process in malaria [5,6,16,21]. Immunoglobulin-E (IgE), which is usually known to be under the influence of IL-4 from Th2 cells, has been seen as the preserve of helminth infection [22]. But total and parasite-specific IgE levels have been reported in cases of malaria which supports the fact that IFN-γ also cause upregulation of low affinity IgE receptor because of IgE elevation [9] and high levels of IgE correlate with protection against severe malaria [9].

Immunology in co-infections of Helminth and Plasmodium species

Helminth trigger Th2 cell differentiation producing IL-4, IL-5, IL-13, IL-9 and IL-25 to obtain effector cells that will induce IgE antibodies from B-cells and further suppress regulator genes of the Th1 arm of the immune response. At the larval phase of early helminth infection, Th1 cells are induced and their fecundity trigger the Th2 usual response [1]. The immune response elicited is dependent on the infection stage just as in the case of malaria parasite infection [5,23], which though it is Th1, activates the Th2 arm at the pre-erythrocytic stage [6,9]. The life cycle of the infecting pathogens together with the cytokine environment determines the response one mounts to helminth, malaria parasites or their co-infections [20]. The questions of how the coexistence of helminths and *Plasmodium* parasites influence the immunological responses to each species need answers [20,23].

Conclusions

The interplay of the various cells after receiving antigens from APCs mainly the CD4+, CD8+, their activated forms and the *TCR-γδ* (has also an APC independent pathway of activation) with their regulatory role through the cytokines and molecules they produce is worth studying in helminth, malaria parasite or their co-infections in an endemic place to unravel the controversies surrounding immune response elicited by their host in more structured studies considering environmental influence.

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Authors contributions

Concept and review carried out by DAG, HD, AB, MTF and BG. Draft essay was written by DAG, reviewed and accepted by all authors.

Declaration

The authors have declared that no competing interests exist.

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